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BERESKIN AND PARR LLP/S.E.N.C.R.L., s.r.l.
40 KING STREET WEST
BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER	
LUM, LEON YUN BON	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/568,409	Applicant(s) LALEV ET AL.	
	Examiner Leon Y. Lum	**Art Unit** 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,29-32 and 34-52* is/are pending in the application.

4a) Of the above claim(s) *29-31,36,41-44 and 47-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,32,34,35,37-40,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Amendment

The amendment to claim 1, filed May 19, 2010, has been acknowledged and entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 32 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Publication No. 2004/0142488 to Gierde *et al.* ("Gierde") in view of U.S. Patent No. 7,379,820 to Sukits *et al.* ("Sukits").

i. Independent claim 1 is obvious

Gierde describes a method for performing affinity chromatography, in which an affinity molecule fixed on a column captures a biomolecule. *See* paragraphs 0083-0092. The biomolecule can be a multi-protein complex. *See* paragraphs 0195-0201; Table 1. With this description, Gierde teaches steps (a)-(b). Gierde also teaches step (c) by describing a wash step. *See* paragraph 0137. One or more constituents of the multi-protein complex can be recovered. *See* paragraph 0200.

Gierde does not, however, teach first and second ligands that associate through electrostatic forces or recovering one of the constituents through decreasing the electrostatic force between it and the rest of the multi-protein complex.

Sukits describes a series of protein pairs – e.g., TRADD and RIP, FAS and FADD, and TNFR-1 and TRADD – that associate together *in vivo* through electrostatic interaction, but can be separated by using NaCl to disrupt the electrostatic interaction. *See* column 18, lines 30-38.

With the foregoing description in mind, one of ordinary skill in the art would have found it obvious to modify Gierde's method to investigate protein-protein interactions in a multi-protein complex using the affinity chromatography assay. By combining Gierde and Sukits, Gierde's method would be modified to include a NaCl elution step on an immobilized protein-protein complex. In this manner, the NaCl elution would separate one protein within the complex from other proteins. The skilled artisan would have been motivated to make the modification because Gierde indicates that the nature of multi-protein complexes can be analyzed by eluting individual components, and the skilled artisan would recognize that reducing electrostatic interaction between proteins is one way of recovering protein constituents. Moreover, because Gierde does not limit the elution to any particular method, the skilled artisan would have had a reasonable expectation of success in combining Sukits's technique with the affinity chromatography method of Gierde.

ii. Dependent claims 32 and 39-40 are obvious

Regarding claim 32, Gierde describes the step of repeating the assay with cell lysates. *See* paragraphs 0138 and 0155.

Regarding claims 39-40, Gierde describes enzyme and polypeptide interactions. See paragraph 0091.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gierde in view of Sukits as applied to claims 1 and 34 above, and further in view of U.S. Patent Application Pub. 2003/0229212 to Fahrner *et al.* ("Fahrner").

NaCl acts as a competitor for heparin, as evidenced by Gierde and Fahrner. Gierde indicates that in ion-exchange chromatography, an analyte can be eluted by displacement using a salt. *See* paragraph 022. Fahrner describes an ion-exchange chromatography as a competition between an ion and a substrate for a molecule of interest. *See* paragraph 0008. Here, NaCl is used as an elution medium against two proteins in a multi-protein complex. *See supra* rejection of claim 1. In light of Gierde and Fahrner, the NaCl competes with the complex to elute a protein in the multi-protein complex, thereby binding to one of the proteins and meeting the claimed limitation.

Claims 1-23, 25-26, 34-35 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rigaut *et al.*, Nature Biotechnology (1999) 17:1030-1032 ("Rigaut"), cited in the IDS filed May 30, 2006, in view of Sukits and Gierde.

i. Independent claims 1-4 are obvious

Rigaut describes a tandem affinity purification method comprising the following steps: (1) fusing DNA encoding a TAP tag to DNA encoding a target protein, thereby creating a construct; (2) introducing the construct into a host cell or organism; (3) expressing the TAP-tagged target protein; (4) preparing an extract with the TAP-tagged target protein (corresponding to the claimed "second ligand"); and (5) performing a two-step affinity purification process in which (i) the TAP-tagged target protein is bound to a first affinity column through a first tag, (ii) the target protein is then cleaved from the first tag and bound to a second affinity column through a second tag, and (iii) the target protein is then eluted from the second column; wherein a wash step is performed after

during each of the separation steps to remove contaminants. *See* page 1030 (entire page). The target protein prior to the affinity separation steps can be bound to another protein (corresponding to the claimed “first ligand”). *Id.* (Figure 1, depicting the target protein attached to "associated proteins"). The TAP-tagged protein and other protein come into contact *in vivo*, prior to the extraction step. *Id.* (describing the tandem affinity purification method as a useful tool to investigate protein complexes). Accordingly, the TAP-tagged protein "associates *in vivo*" with the other protein as claimed.

With the above description, Rigaut teaches steps (a)-(c) of claim 1, steps (a)-(e) of claim 2 and steps (a)-(h) of claim 3. Moreover, regarding claim 4 and the claimed “fusion protein complex comprising two or more subunits of which are fused to different affinity tags that can selectively bind to different affinity matrixes,” this limitation is interpreted to include multiple proteins since the second ligand is defined in the claims as a protein complex. Rigaut indicates that the two tags can be placed on different proteins in a complex. *See* page 1031 (right column, second paragraph). Accordingly, Rigaut teaches steps (a)-(h) of claim 4.

Rigaut does not, however, teach first and second ligands that associate through electrostatic forces or a step of separating the first and second ligands by decreasing the electrostatic force between them (i.e., step (d) of claim 1, step (e) of claim 2, step (i) of claim 3 and step (i) of claim 4).

Sukits describes a series of protein pairs – e.g., TRADD and RIP, FAS and FADD, and TNFR-1 and TRADD – that associate together *in vivo* through electrostatic

interaction, but can be separated by using NaCl to disrupt the electrostatic interaction. *See* column 18, lines 30-38.

Gierde describes eluting protein constituents from a multi-protein complex, in order to analyze the nature of the complex. *See* paragraph 0201. The complex is bound to an affinity column. *See* paragraph 0196.

With the foregoing description in mind, one of ordinary skill in the art would have found it obvious to modify Rigaut's method to investigate protein-protein interactions in multi-protein complexes using electrostatic elution. By combining Rigaut with Sukits, Rigaut's method would be modified to include a NaCl elution step on a multi-protein complex. In this manner, the NaCl elution would separate at least one protein constituent from other proteins in the complex. The skilled artisan would have been motivated to make the modification because Gierde indicates that the nature of multi-protein complexes can be analyzed by eluting individual components, and the skilled artisan would recognize that reducing electrostatic interaction between proteins is one way of recovering protein constituents. Moreover, because Gierde indicates that different types of elutions can be used in affinity chromatography, the skilled artisan would have had a reasonable expectation of success in combining Sukits and Gierde's technique with the tandem affinity separation method of Rigaut.

ii. Dependent claims 5-23, 25-26, 34-35 and 38 are obvious

With respect to claim 5, Gierde teaches an antibody affinity molecule that binds to a protein antigen within a multi-protein complex. *See* Table 1.

With respect to claims 6-7, 14-15 and 20-21, the TAP tag comprises Staphylococcus Protein A that can bind to IgG. *See* Rigaut, page 1030; Figure 1. Regarding claims 20-21, it would have been obvious to one of ordinary skill in the art to use protein A as either the first or second affinity ligand - i.e., switch positions with calmodulin binding peptide, since the purpose of Rigaut is simply to utilize dual-dimension affinity chromatography. Indeed, the genetic procedure to recombinantly produce the TAP tag could have placed protein A closer to the target protein.

With respect to claims 8-9 and 16-19, the TAP tag comprises calmodulin binding peptide, which can be separated from the protein via EGTA. *Id.* Moreover, TEV protease is used to cleave protein A from the calmodulin binding peptide. *Id.* Regarding claims 16-19, it would have been obvious to one of ordinary skill in the art to use the calmodulin binding peptide as either the first or second affinity ligand - i.e., switch positions with protein A, since the purpose of Rigaut is simply to utilize dual-dimension affinity chromatography. Indeed, the genetic procedure to recombinantly produce the TAP tag could have placed calmodulin binding peptide closer to the target protein.

With respect to claims 10-11, TEV protease is used to cleave the TAP-tagged protein from the first affinity separation column. *Id.*

With respect to claim 12, Gierde describes that an extraction step which removes analyte from the affinity column can involve binding of the analyte to a specific cognate molecule. *See* paragraph 0143. One of ordinary skill would have found it obvious to use the same antibody coated on the affinity column as the specific cognate molecule.

Indeed, because the coated antibody has known affinity for the analyte, the skilled artisan would have recognized that using the same antibody for the specific cognate molecule would produce the extraction sought.

With respect to claim 13, Gierde describes a method of performing step elutions, in which sequential elutions are performed using different types of gradients. *See* paragraphs 0181-0187. The gradients can be in any order and not required to be performed in a particular sequence. *See* paragraph 0185 (describing a first elution by increasing ionic strength and a second elution by affinity binding, but not limited to these specific elution gradients).

With the foregoing description in mind, one of ordinary skill in the art would have found it obvious to modify Rigaut and Sheehan’s method by performing sequential elutions using ionic strength and affinity binding in that order. In making the combination, Rigaut and Sheehan’s method of sequential Protein A and calmodulin binding peptide would be reversed – i.e., the first affinity separation would utilize calmodulin binding peptide and the second affinity separation would utilize Protein A. Because Rigaut teaches a split TAP tag that places the two tags on different subunits, the skilled artisan would have recognized that Gierde's teaching of sequential elutions can be applied to bind the protein complex using the tags in any order. Accordingly, it would have been obvious to modify Rigaut and Sheehan's method using Gierde in the manner described. The skilled artisan would have made the modification because Rigaut indicates that TAP is an alternatively way of performing tandem affinity separation, *see supra* rejection of claim 4, and Gierde implies that two dimensional

separations can be performed using a variety of elutions not in any particular order. Moreover, because all references are directed to affinity column separation, the skilled artisan would have had a reasonable expectation of success in combining the references.

With respect to claims 22 and 23, the NaCl gradient incorporates an increasing ionic strength gradient, especially since the objective is to separate one protein from the other. *See supra* rejection of claim 1.

With respect to claims 25 and 26, because Sukits describes an NaCl elution medium, it would have been obvious to one of ordinary skill in the art to select a change in concentration using the ranges claimed. Indeed, the skilled artisan would have arrived at the claimed ranges based on the doctrine of routine optimization. In a case decided by the precursor to the Federal Circuit, the court stated that a claim is not allowable where the skilled artisan could have arrived at the claim through routine experimentation on the optimum or workable ranges of the claim. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (stating "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.") In *Aller*, the claims were directed to a process taught by the prior art, except for a specific temperature and acid concentration range. *Id*. The court held, however, that the claims were not patentable because the skilled artisan could have arrived at the claimed ranges through routine optimization. Similar to that case, Rigaut, Sukits and Gierde teach all the limitations of claims 25 and 26, except for a concentration range. Lacking evidence to the contrary, it would have been within the

routine skill of the skilled artisan to optimize the concentration ranges of the NaCl elution compound to arrive at the claimed ranges.

With respect to claim 34, NaCl is capable of separating one protein from the other, thereby having “capability” to separate the “first ligand from the second ligand,” as claimed. *Id.*

With respect to claim 35, Sukits describes a mutation. *See* column 18, lines 43-45. As held by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (U.S. 2007), an obvious to try rationale is proper, given a "finite number of identified, predictable solutions.” *KSR* at 1397. Indeed, the Court stated that in such a case, “a personal of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id*. Here, as would have been recognized by one of ordinary skill in the art, it would have been obvious to try a mutated FADD protein in order to analyze the interaction of the protein with FAS.

With respect to claim 38, one of ordinary skill in the art would have found it obvious to include an electrostatic charge identical to a mutation (species (b) in the claim) since the object of the combination of Rigaut, Sukits and Gierde is to separate the protein constituents. Moreover, because Rigaut teaches a gradient, *see supra* rejection of claim 1, the skilled artisan would have found it obvious to include the claimed electrostatic charge in the range of NaCl concentrations.

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rigaut in view of Sukits and Gierde as applied to claims 1 and 22-23 above, and further in view of

U.S. Patent No. 5,007,934 to Stone and U.S. Patent No. 5,849,885 to Nuyens *et al*. ("Nuyens").

Rigaut, Sukits and Gierde (together "Rigaut") do not teach a KCl chemical agent.

Stone describes using NaCl or KCl as equivalent salts for removing glycoprotein or proteoglycan associated with collagen through electrostatic interaction. *See* column 7, lines 60-66.

Nuyens describes NaCl or KCl as equivalent salts for reducing electrostatic interactions between lactoferrin and other proteins. *See* column 4, lines 51-60.

With the foregoing description in mind, one of ordinary skill in the art would have found it obvious to modify Rigaut's method to use KCl as the eluting compound instead of NaCl. The skilled artisan would have performed the modification because it is well known in the art to use KCl as a substitute for NaCl for disrupting electrostatic interactions between proteins, as evidenced by Stone and Nuyens. For the same reason, the skilled artisan would have had a reasonable expectation of success in substituting KCl for NaCl.

Claims 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rigaut in view of Sukits and Gierde as applied to claim 1 above, and further in view of U.S. Patent 6,610,508 to Hentze *et al.* ("Hentze") and evidenced by U.S. Patent No. 5,753,225 to Clary *et al.* ("Clary").

Rigaut, Sukits and Gierde (together "Rigaut") do not teach the step of identifying protein-protein association as a putative cause for Alzheimer's disease.

Clary describes receptor-ligand complexes as reversible electrostatic attractions. *See* column 10, lines 66-67; column 11, lines 1-11.

Hentze describes a step of identifying protein-protein interactions in order to detect disease states, including Alzheimer's disease. *See* column 1, lines 33-54; column 30, lines 58-62,

With the foregoing description in mind, one of ordinary skill in the art would have found it obvious to modify Rigaut's method to include the step of identifying protein-protein interactions for detecting Alzheimer's disease. The skilled artisan would have made the modification because detecting Alzheimer's disease informs a patient whether the disease state is present. Moreover, the skilled artisan would have had a reasonable expectation of success because protein-protein interaction is a type of ligand-receptor interaction, which is known to be a reversible electrostatic attraction. *See* Clary, column 11, line 10. Hentze's technique would therefore fit well with Rigaut's method utilizing electrostatic interactions.

Response to Arguments

Applicants traverse the rejections of the Office Action dated February 19, 2010 in the Response filed May 19, 2010. Applicants make a number of arguments against the cited prior art references. After fully considering these arguments, they are not found to be persuasive for the following reasons (grouped in the same order they were addressed in the Response).

i. <u>Claims 1, 32 and 39-40</u>

Applicants opine that cited portions of the Gierde reference, particularly paragraphs 0195-0201, are inapplicable because the reference's filing date is after the priority date of the instant application and allegedly none of the reference's priority documents support the cited paragraphs. *See* Response, page 13 (traversing the previous Office Action's assertion that Gierde describes multi-complex proteins in vivo). However, a close inspection of priority document Provisional Application No. 60/396,595 reveals a description of recombinant fusion proteins separated using affinity chromatography. *See* pages 72-73, corresponding to Affinity Chromatography: Principles and Methods, page 42 (in the section titled "Recombinant fusion proteins"). Accordingly, the '595 application provides sufficient support for Gierde's description of multi-complex proteins separated using an affinity column. Paragraphs 0195-0201 are therefore appropriate prior art citations.

Applicants also argue that Gierde and Sukits are directed to different a chromatography method from the claimed method. *See* page 11, second paragraph. Specifically, Applicants state that both Gierde and Sukits allegedly only teach the following method: purifying the second ligand, coupling it to a solid support by covalent bonds and then applying a biological sample containing the first ligand. *Id.* Applicants argue that this method is distinct from the claimed method, which requires non-covalent bonds and contacting the first and second ligand prior to binding the second ligand to the affinity column. Gierde, however, is not limited to the method alleged by Applicants. Indeed, as noted in the rejection *supra*, Gierde is relied upon to teach the binding of multi-complex proteins onto an affinity column. *See supra* rejection of claim 1. With this

description, Gierde therefore uses affinity binding as opposed to covalent bonding and teaches first and second ligands in contract prior to contacting the affinity column, all in conformity with the claimed invention. Moreover, since Gierde already teaches multi-complex affinity chromatography, Sukits is not relied upon for the same teaching, but primarily for its teaching of disrupting electrostatic interactions between proteins that come together in vivo. Accordingly, Gierde and Sukits together teach the claimed invention.

Applicants, moreover, argue that Gierde and Sukits only teach in vitro formation of protein complexes. *See* page 12, first paragraph. However, Gierde describes natural protein complexes. *See* paragraphs 0198-0199. Furthermore, these natural protein complexes are supported by the recombinant fusion proteins described in the ‘565 application, as noted above

Applicants also take issue with Gierde’s statement that “some subset of complex is released while the rest remains absorbed,” arguing that this statement is too vague and does not provide guidance that would lead to the presently claimed method. *See* Response, page 14, first paragraph. Taken with Sukits, however, one of ordinary skill in the art would recognize that disrupting electrostatic interactions between proteins would allow the proteins not attached to the chromatography column to be released into solution while the proteins attached to the chromatography column will remain bound to their affinity counterparts. Accordingly, read in combination, Gierde and Sukits provide the appropriate guidance to the skilled artisan to elute some proteins while keeping others attached firmly to the affinity chromatography column.

Applicants further assert that Gierde provides two examples that allegedly teach away from the claimed invention. *See* page 14, first paragraph (describing decreasing the polarity of a desorption solvent and adding a reducing agent). Sukits, however, is not directed at either technique – neither a reducing agent nor a solvent changing polarity is used to cause elution of a protein. Indeed, Sukits is directed to decreasing electrostatic interactions between proteins.

Applicants' arguments against claims 1, 32 and 39-40 are therefore not convincing to overcome the cited prior art.

ii. <u>Claim 37</u>

Applicants opine that Fahrner fails to remedy the alleged deficiencies of Gierde and Sukits. However, as note above, neither Gierde nor Sukits are deficient. Accordingly, Applicants' argument is not convincing.

iii. <u>Claims 1-23, 25-26, 34-35 and 38</u>

Applicants reassert their argument that Gierde's teachings in paragraphs 0195-0201 do not antedate the priority date of the instant application. *See* page 15, fourth paragraph. However, as noted above, the '595 application describes multi-complex proteins and therefore provides support for these paragraphs.

Applicants also argue that Rigaut teaches desorption of the second protein from the affinity column by describing SDS-PAGE electrophoresis, thereby distinguishing itself from the claimed invention since the second protein would also dissociate from the affinity column. *See* page 16, first paragraph. In a similar light, Applicants argue that Rigaut and Gierde's purpose is not to prove the association of first and second ligands

in vivo. *See* page 16, last paragraph. Applicants' arguments appear to be directed at Rigaut and Gierde alone. However, neither Rigaut nor Gierde are cited alone in the rejection. Indeed, Rigaut is modified by Gierde and Sukits. As noted by Applicants, Gierde describes a process of keeping some proteins bound to the affinity column while eluting others. Combining Rigaut and Gierde produces the situation in which some proteins are eluted while others remain attached to the column; in this manner, specific proteins in a complex can be isolated for further study. Since Sukits describes one manner in which proteins in a complex can be separated through decreasing electrostatic interaction, this method combined with Rigaut and Gierde's teachings produces the situation in which the affinity-interactions between proteins in a complex will allow those proteins to remain bound to the column while other proteins electrostatically attached to the bound proteins will be eluted. Accordingly, together, Rigaut, Gierde and Sukits teach a method for eluting specific proteins that are electrostatically bound in a protein complex.

Applicants' arguments are therefore not convincing.

iv. <u>Claim 24</u>

Applicants opine that Nuyens fails to remedy the alleged deficiencies of Rigaut, Gierde and Sukits. However, as note above, Rigaut, Gierde and Sukits are not deficient. Accordingly, Applicants' argument is not convincing.

v. <u>Claims 45 and 46</u>

Applicants opine that Hentze and Clary fail to remedy the alleged deficiencies of Rigaut, Gierde and Sukits. However, as note above, Rigaut, Gierde and Sukits are not deficient. Accordingly, Applicants' argument is not convincing.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y. Lum whose telephone number is (571) 272-2872. The examiner can normally be reached on Monday to Friday (8:30 am to 5:00 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon Y. Lum/
Examiner, Art Unit 1641

/Unsu Jung/
Primary Examiner, Art Unit 1641